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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,388	12/12/2001	Kevin P. Baker	GNE.2830P1C44	9957

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EXAMINER	
TURNER, SHARON L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,388	BAKER ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-17-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-27 have been canceled and claims 28-47 have been added as requested by Applicant in the Preliminary Amendment filed December 12, 2001.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), 120 and 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's have amended the first line of the specification as directed in the preliminary amendment. The amendment identifies multiple applications upon which priority is claimed. Applicant's have also submitted a priority map that identifies particular applications in which PRO1295 (SEQ ID NO's:53-54) are disclosed. However, utility is not granted based upon detection in the gene amplification assay as set forth herein. As the priority lineage does not establish compliance with the requirements of 35 USC 112, first paragraph, the effective filing date awarded instant claims is that of the instant filing date, 12-12-01.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page

numbers of any parent application filed prior to12-12-01 which specifically supports the claim limitations for each and every claim limitation in all the pending claims which Applicant considers to have been in possession of and fully enabled for prior to 10-15-01. The utility and enablement of the invention should also be addressed as noted below.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

4. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Double Patenting

5. Applicant and the assignee of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary to the examination of this application. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application.

A sequence search of the pending and published application databases has revealed that there are a series of applications in which SEQ ID NO: 53 is present but that do not claim the polynucleotide. However, there is at least one other application

filed by the applicants which contains the polynucleotide of SEQ ID NO: 53 which is identical to the polypeptide of SEQ ID NO: 54, and which may contain possible conflicting claims. Due to the large number of applications that contain this sequence, the examiner is unable to determine if any of these applications have claims directed to this polynucleotide. Applicant is required to point out to the Examiner all double patenting issues. See MPEP § 1.105.

The applicant is reminded that the reply to this requirement must be made with candor and good faith under 37 CFR 1.56. Where the applicant does not have or cannot readily obtain an item of required information, a statement that the item is unknown or cannot be readily obtained will be accepted as a complete reply to the requirement for that item.

This requirement is a requirement set forth within the instatnt Office action. A complete reply to the enclosed Office action must include a complete reply to this requirement. The time period for reply to this requirement coincides with the time period for reply to the enclosed Office action.

Formal Matters

4. The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see MPEP Chapter 2400 and 37 C.F.R."1.801-1.809). Examiner acknowledges the deposit of organisms under accession number ATCC 203287 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in compliance with this requirement (see specification, page 517).

Claim Rejections - 35 USC § 101 and § 112

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 28-47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 28-47 are directed to the nucleic acid of SEQ ID NO: 53 encoding the protein of SEQ ID NO: 54, identified as PRO1295. The instant specification discloses that PRO1295 is a 280 amino acid protein with signal peptide at about residues 1-18. A targeting signal and N-glycosylation site are also noted. The molecular weight is approximates 30,163 daltons with an estimated pI of 6.87. The Figure 32 further identifies that the peptide has the following characteristics; Signal peptide: amino acids 1-18, N-glycosylation site: amino acids 244-248, cAMP- and cGMP-dependent protein kinase phosphorylation site: amino acids 89-93, Casein kinase II phosphoryiation site: amino acids 21-25, 167-171, 223-227, N-myristoylation site: amino acids 100-106, 172-178, 207-213 and Microbodies C-terminal targeting signal: amino acids 278-282. The specification notes homology to various accession numbers but fails to note the specific similarity or the proposed function for PRO1295 or any of the noted homologous segments. The specification further notes testing for the nucleic acid sequence within the gene amplification assay 143 at pp. 506-507 where it is noted that the PRO 1295 sequence was detected with a change in concentration or doubling within particular (but

not all) primary tumor cell lines including lung, colon and breast. No other positive assay is noted for PRO1295.

The claims are directed to isolated nucleic acids having at least 80%, 85%, 90%, 95% or 99% sequence identity to a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 53, with or without its signal peptide, or to the extracellular domain of SEQ ID NO: 53 with or without its signal peptide. Dependent claims are directed to vectors and host cells comprising the isolated nucleic acids. The specification contains numerous asserted utilities for the polypeptide and encoding nucleic acids, including use as hybridization probes, in chromosome and gene mapping, in the generation of anti-sense RNA and DNA, to identify molecules that bind to PRO (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. However, the utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) do not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO1295 sequence or any activity specifically associated therewith.

The Gene amplification assay is not noted to evidence specific and substantial asserted utility or well established utility because the noted expression is not prescribed to any reasonably likely indication. Given that PRO1295 sequences was amplified in only a very small number of tumors, and not in tumors of the same type, or all tumors, the data do not support the implicit conclusion that the sequences shows positive correlation sufficient to specifically identify lung, colon or breast cancer. Cancerous

tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Even if the data were corrected for aneuploidy, one of ordinary skill in the art would not conclude that PRO1295 would be diagnostic for lung, colon or breast cancer, due to the lack of overexpression in the majority of primary tumor cell types.

Even if the data demonstrated a increase in copy number of PRO1295 nucleic acids in primary tumors, such would not be indicative of a use of the encoded polypeptide as a diagnostic agent. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Also, it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the protein would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95:14717-14722) teach that

> "An analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP-3* RNA was seen in the absence of DNA amplification. In contrast, *WISP-2* DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See page 14722, second paragraph of left-hand column; pp.14720-14721; Pages 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors". Gygi et al. (Molecular and Cellular Biology, March 1999, p. 1720-1730),

studied over 150 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. Gygi et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (abstract and Figure 5).

Thus, the data do not support the implicit assertion that the nucleic acids of PRO1295 or the encoded polypeptide can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO1295 is overexpressed in any cancer to the extent that the nucleic acids or polypeptides could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

Accordingly, while described via SEQ ID NO: structure, the protein and encoding nucleic acids are not evidenced as providing for any specific and substantial asserted utility, or well established utility. No significance or beneifit is prescribed or evidenced for the claimed sequences and their use.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 28-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Even if

the specification were enabling of how to use the PRO1295 nucleic acids, enablement would not be found commensurate in scope with the claims. If one of skill in the art does not know how to use the nucleic acids or proteins the skilled artisan would clearly not know how to use nucleic acid molecules that are 80-99% identity to a nucleotide sequence encoding the polypeptide of SEQ ID NO: 54 or nucleic acids that hybridize to a nucleotide sequence encoding the polypeptide.

9. Claims 28-33, 36-37 and 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes polynucleotides encoding the peptide sequence consisting of SEQ ID NO:54, which is shown to test positive in the gene amplification assay as noted above. However, the claims as written include polynucleoitdes encoding polypeptides having at least 80-99% sequence identity with SEQ ID NO:54 and polynucleotides encoding polypeptides including or lacking various regions including; lacking its signal peptide, comprising the extracellular domain, and comprising the extracellular domain but lacking its signal peptide, and nucleic acids that hybridize but for which no particular biological activity, function or hybridization stringency conditions are recited. Further, while the specification and claims refer to Figure 32, no definitive direction is provided as to those portions of the sequence which constitute

extracellular portions. Thus, the claims are directed to various generic and sub-generic recitations lacking in identified and correlative structure and function.

However, the instant disclosure of a single polynucleotide encoding a polypeptide, that of SEQ ID NO's :53 and 54, with no disclosed activity, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan

for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus.

However, the instant specification discloses only the single sequences of SEQ ID NO:53 and 54 and no other members of the claimed genus sharing particular function. Given the unpredictability of homology comparisons, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and the fact that the specification fails to provide objective evidence of any additional sequences with the same requisite function, it cannot be established that a representative number of species have been disclosed to support the genus claim. No activity is set forth for the additional sequences and there is no evidence for a correlation or nexus provided between possession of any homologous feature and any activity as noted such that it is clearly conveyed that possession of any polypeptide having such structural similarity would possess the same function. Thus, the claims lack adequate written description support.

In addition to the aforementioned defects with respect to 112, first paragraph as noted above, the following deficiencies are noted even should utility be found.

10. Claims 28-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the variable encoding sequences and for such generic sequences where no requisite functional activity is provided as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses identification of SEQ IDNO:53 in the gene amplification assay but no other activity associated with the structure and function of the

molecule that is noted to encode SEQ ID NO:54. However, the specification further fails to note such conserved activities in any 80-99% variable molecule and fails to teach the significance or use of such modified sequences. However, applicants claims are directed to peptides with 80-99% homology, to extracellular domains and to sequences lacking the signal peptide where no requisite function is required.

The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polynucleotides encoding the polypeptides retain sufficient structural similarity to evoke activity. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation among homologous sequences. Moreover, no similar function is required of the additional sequences. The artisan would be unable to determine how to use such similar sequences that lack common function. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int.

1986).

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-47 are directed to isolated peptides comprising "the extracellular domain" and "lacking its associated signal peptide". The specification generally teaches that the PRO "extracellular domains" are a form of the PRO polypeptide "which is essentially free of the transmembrane and cytoplasmic domains." Yet Figure 32 fails to teach any extracellular residues. There is no description of the folded protein, extracelluar sequences or regions of the peptide which would be extracellular. These limitations cannot be read into the claims and the specification fails to teach the orientation of the molecule with respect to the intracellular and/or extracellular portions.

Further, the claim is directed to the extracellular domain lacking its associated signal peptides. However, signal peptides are not generally considered to be "associated with" extracellular domains and indeed in this particular incidence they are

not identified as being adjacent. Thus, the metes and bounds of the recitations are indefinite with respect to those residues that are intended to be included or excluded by the claim recitations and the artisan is not provided definitive guidance whereby the residues may be determined.

Moreover, the claims are drawn to hybridizing sequences and to hybridization under stringent conditions. However, hybridization is variable depending on the conditions, see in particular Sambrook et al., Cold Spring Harbor Labs 1989, pp. 9.47-9.51 and 11.48-11.49. Those conditions that are deemed to be "stringent" vary in the art and are undefined in the specification. Accordingly, the metes and bounds of the residues included or excluded by the noted recitations is indefinite. Clarification of the particular amino acids and hybridization conditions are required.

Conclusion

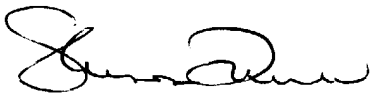
13. No claims are allowed.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.



SHARON L. TURNER, PH.D.
PATENT EXAMINER

Sharon L. Turner, Ph.D.
September 30, 2004